REMARKS

In the Specification:

Applicant thanks the Examiner for withdrawing the objections to the specification raised in the Office Action of March 24, 2003.

In the Claims:

Applicant has cancelled claims 1-27 herein without prejudice or disclaimer. Applicant has added new claims 28-34. New claims 28-34 do not encompass new matter and are supported throughout the specification, including at page 31, lines 9-15, page 33, lines 11-20, and at pages 119-137.

Priority Determination:

The Examiner contends that the effective priority date for the present application is December 1, 1999, the filing date of PCT/US99/28301. Applicant respectfully disagrees. The present application has utility and is enabled for use as a diagnostic for a tumor in a tissue, which was disclosed in provisional application 60/113,296, filed December 22, 1998. Therefore the proper priority date for the present invention is December 22, 1998.

Specifically, as stated in the previous Response and Request for Reconsideration mailed June 24, 2003, 60/113,296 describes three specific uses for the claimed invention: (1) as part of ribozyme and/or triple helix sequences which, in turn may be used in regulation of amplified genes (page 3, lines 23-25); (2) for determining the presence of PRO347 (page 3, lines 26-32); and (3) for diagnosing a tumor by detecting the level of expression of a gene encoding PRO347 (page 3, lines 33-35 – page 4, lines 1-24). Further, at pages 23-28, 60/113,296 discusses detecting gene amplification/expression of PRO347 in certain tissues and at pages 28-29, 60/113,296 describes anti-PRO347 antibody binding studies, which may be used to detect the polypeptide of SEQ ID NO:50.

Moreover, at pages 55-101, 60/113,296 describes methods for determining whether the genes encoding various PRO polypeptides are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. As with U.S. Application Serial No. 09/944,896, the gene amplification examples measure and discuss Δ Ct values.

Table 2, found at pages 65-72 sets forth the Δ Ct values for various PRO polypeptides in various tissues. The Δ Ct values for PRO347 are listed in the 8th column from the top, left-hand side of the page. This data demonstrates that the PRO347 gene is amplified in cancerous tissues. The results of the gene amplification study with respect to PRO347 are discussed at page 105, lines 22-33. Amplification of PRO347 DNA was detected in various tumors and therefore, as stated at page 105, lines 32-33, "antagonists, (e.g. antibodies) directed against the protein encoded by DNA44176 (PRO347) would be expected to be useful in cancer therapy." Those of skill in the art would also recognize that the nucleic acid encoding the protein associated with cancer, as well as the protein itself would also have diagnostic utility.

The Examiner's priority determination is based on her finding that the claimed invention is not supported by either a specific and substantial or a well-established utility. Applicant addresses the Examiner's concerns regarding utility below under the heading 35 U.S.C. § 101 and § 112 and respectfully requests the Examiner also consider those arguments in determining priority.

Claim Rejections:

35 U.S.C. § 102(e)

The Examiner has rejected claims 22-26 under 35 U.S.C. § 102 (e) as being anticipated by Holtzman *et al.*, U.S. Patent Application Publication US20020028508, effective filing date, April 23, 1998. Specifically, the Examiner alleges that Holtzman *et al.* disclose a protein that is 96.8% identical to the protein of SEQ ID NO: 50, particularly amino acids 27-109 of SEQ ID NO:50 and given that high degree of identity, any antibody that would bind to the protein of the instant invention, would also bind the protein of Holtzman *et al.*

Applicant respectfully disagrees that Holtzman *et al.* anticipates the claimed invention. First, "[t]o serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. 'A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosure cited as prior art is not enabled.'" *See Elan Pharm., Inc. v. Mayo Found. For Med. Ed. and Research,* 2003 U.S. App. LEXIS 20195 (Fed. Cir. 2003) citing *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). Applicants submit that Holtzman *et al.* is not enabled because the nucleic acid, protein and antibody cited by the Examiner (hereinafter collectively referred to as "T139") are not supported by either a specific and substantial utility or a well-established utility.

Specifically, Holtzman *et al.* discloses both the nucleic and amino acid sequences of T139 and reference a deposit of a cDNA (ATCC 98694). As the Examiner notes, the nucleic acid sequence disclosed by Holtzman *et al.* is 94.1% identical to the nucleic acid molecule of SEQ ID NO:49 and the amino acid sequence disclosed by Holtzman *et al.* 96.8% identical to the protein of SEQ ID NO:50. Much like the present specification, Holtzman *et al.* discloses various characteristics of the cDNA sequence encoding T139, as well as various predicted characteristics of the T139 protein (p. 8, paragraph 0107). Also much like the present specification, Holtzman *et al.* discloses that sequence analysis revealed various homologies, for example T139 is described as homologous to testis-specific protein-1 (TPX-1) (page 8, paragraph 0110). Holtzman *et al.* also explains generally various variant T139 sequences, antibodies to T139, assays, and methods of treatment. In addition, Holtzman *et al.* discloses the isolation and characterization of T139 cDNA, the distribution of T139 mRNA in human tissues and the predicted characterization and production of T139 proteins. However, unlike the present specification, Holtzman *et al.* does not enable one of skill in the art to use T139. Specifically, although Holtzman *et al.* generally notes that T139 might be used to modulate the function, morphology, proliferation and/or differentiation of cells in tissues in which it is expressed (p. 39, paragraph 0367), or used to treat renal (kidney) disorders (p.39-40, paragraph 0375), or used to treat testicular disorders (p. 40, paragraph 0376), Holtzman *et al.* does not disclose any working example of a credible,

specific and substantial utility for T139. Hence, Applicant submits that Holtzman *et al.* does not enable that which it is asserted to anticipate and therefore, does not anticipate the present invention.

In addition, Applicant has cancelled claims 22-26 without prejudice or disclaimer. Currently pending claims 28-34 are directed to methods for detecting or purifying a polypeptide encoded by a nucleic acid that is amplified in lung or colon tumors comprising contacting a lung or colon tissue sample from a mammalian subject with an antibody that specifically binds to the polypeptide shown in Figure 20 (SEQ ID NO:50). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.01. Holtzman *et al.* neither explicitly nor inherently discloses methods for detecting or purifying polypeptides encoded by a nucleic acid that is amplified in lung or colon tumors and therefore, cannot anticipate these claims.

Rather, Holtzman *et al.* teaches that T139 is homologous to testis-specific protein (see p. 8, paragraph 0110) and plays a role in kidney defects such as kidney failure or hyperplasia (see p. 38, paragraph 0359). Holtzman *et al.* does not disclose or examine the presence of T139 protein or nucleic acid in lung or colon tumor tissue. Instead, at page 41, paragraph 0397, Holtzman *et al.* discloses that mRNA encoding the protein cited by the Examiner is expressed at high levels in the kidney with lower levels in the testis but that "[n]o other tissue examined (heart, brain, placenta, **lung**, liver, skeletal muscle, pancreas, spleen, thymus, ovaries, small intestine, **colon** and peripheral blood leukocytes) showed any expression." (emphasis added). *See also* p. 8, paragraph 0113. Thus, for this additional reason, Holtzman *et al.* does not anticipate the present claims, which are directed to methods for identifying and purifying a polypeptide that is encoded by a nucleic acid which is amplified in lung and colon tumors. Hence, Applicant has overcome this ground of rejection and respectfully requests that it be withdrawn.

35 U.S.C. § 101 and § 112

Previously pending Claims 22-26 were rejected under 35 U.S.C. § 101 because the Examiner maintained that the claimed invention was not supported by either a specific and substantial asserted utility or a well established utility. Applicant notes that the Examiner based her rejection on her careful consideration of the Goddard Declaration. Specifically, the Examiner stated that the declaration addressed her concerns regarding the significance of a difference of 1 or 2 PCR cycles, as well as her concerns regarding whether proper controls for aneuploidy were used, and therefore, the Examiner concluded that the nucleic acid molecule of SEQ ID NO:49 would have utility, and would be enabled as being useful as a probe to diagnose certain cancers. However, the Examiner noted that the claims of the present application were directed to antibodies. Thus, the Examiner, citing Pennica *et al.,* asserted that it does not necessarily follow that an increase in gene copy number results in increased gene and protein expression.

Applicant has canceled claims 22-26 without prejudice or disclaimer. Currently pending claims 28-32 are supported by a substantial, specifically asserted utility. See, for example, page 137, lines 22-24, stating that "antagonists (*e.g.* antibodies) directed against the proteins encoded by the DNAs tested would be expected to have utility in cancer therapy and as useful diagnostic reagents." An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See also In re Jolles*, 638 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (9165); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-213 (CCPA 1977).

Moreover, in order to satisfy the utility requirement of 35 U.S.C. § 101, Applicant need only provide one credible assertion of specific and substantial utility for each claimed invention. The credibility of the asserted utility is to be assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed

publications) that is probative of Applicant's assertions. MPEP § 2107-II(B)(ii) (8th ed. 2001).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the Applicant. The issue will then be decided on the totality of the evidence.

In the present case a *prima facie* case of lack of utility has not been established. First, one basis for the Examiner's previous conclusion of lack of utility is based on a quote from Pennica *et al*, cited in the Goddard Declaration, which was filed with and discussed in Applicant's Amendment and Request for Reconsideration mailed June 24, 2003. Based on this reference, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation between gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack of correlation observed for the family of polypeptides referenced in Pennica *et al.* is typical, or is merely a discrepancy, an exception to the rule of correlation.

Moreover, the totality of the evidence demonstrates that the present claims are supported by a specific and substantial utility. Specifically, even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a

gene that is amplified in cancer would still have a specific and substantial utility. Enclosed herein is a declaration of Avi Ashkenazi, Ph.D., an expert in the biology of cancer and an inventor of the present invention. As Dr. Ashkenazi explains at paragraph 6 of his declaration:

> [E]ven when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression of the corresponding gene product still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, methods of detecting or purifying a polypeptide encoded by a nucleic acid that is amplified in lung and/or colon tumors are supported by a substantial, specific utility. Applicant respectfully requests that the Examiner withdraw the present rejection of claims 22-26 and submits that this rejection is improper with respect to presently pending claims 28-34 because the claimed invention has utility and is fully enabled.

35 U.S.C. § 112, first paragraph

Claims 22-26 remain rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement based on the Examiner's maintaining her position that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicant submits that as explained above, presently pending claims 28-34 are supported by both a specific and substantial utility and a well established utility. Therefore, this ground of rejection has been overcome and Applicant respectfully requests that it be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 22-26 are rejected under 35 U.S.C. § 112, second paragraph , as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that it is not clear what "specifically binds" means.

Applicant has canceled claims 22-26 without prejudice or disclaimer. Currently pending claims 28-34, however, also recite "specifically binds." Applicant disagrees that this term is indefinite. According to MPEP §2173.02, "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of: (a) the content of the particular application disclosure; (b) the teachings of the prior art; and (c) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." As Applicant stated previously, the term "specifically binds" is used in a context which is consistent with the understanding of one of ordinary skill in the art, at pages 16, 82, 88 and 116 of the application. For example, at page 82 of the specification, Applicant uses "specifically binds" to refer to an antibody that is manufactured with the characteristic of binding to a particular agent:

> In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent.

Moreover, Example 24, beginning on page 116, describes the preparation of antibodies that *specifically* bind PRO polypeptides. Finally, if the meaning of a claim term is not clear from a claim, then objective resources, such as dictionaries and treatises, may be consulted to understand the ordinary meaning of a claim term to one of skill in the art at the time of filing. *Texas Digital v. Telegenix, Inc.*, 308 F.3d 1193, 1202-03 (Fed. Cir. 2002). Hence, Applicant submits that "specifically binds" is not indefinite because the scope of the claims can be determined with a reasonable degree of certainty.

35 U.S.C. § 102(a)

Claims 22-26 are rejected under 35 U.S.C. § 102(a) as being anticipated by Botstein *et al.*, WO 99/35170, published July 15, 1999 and as being anticipate by Holtzman *et al.*, 99/54343, published October 28, 1999. Applicant has canceled claims 22-26 and therefore, has overcome this rejection. Moreover, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, before either Botstein *et al* or Holtzman *et al* were published. Therefore, neither reference may be properly cited against the instant application under 35 U.S.C. § 102(a).

SUMMARY

Applicant believes that currently pending Claims 28-34 are patentable. Applicant respectfully requests the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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APPENDIX A

OIPE JC10 DEC 24 2003 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ashkenazi et al.
App. No.	:	09/903,925
Filed	:	July 11, 2001
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Hamud, Fozia M

Group Art Unit 1647

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner of Patents, Washington D.C. 20231 on:

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(Date)

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Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF AVI ASHKENAZI, Ph.D UNDER 37 C.F.R. § 1.132

I, Avi Ashkenazi, Ph.D. declare and say as follows: -

1. I am Director and Staff Scientist at the Molecular Oncology Department of Genentech, Inc., South San Francisco, CA 94080.

2. I joined Genentech in 1988 as a postdoctoral fellow. Since then, I have investigated a variety of cellular signal transduction mechanisms, including apoptosis, and have developed technologies to modulate such mechanisms as a means of therapeutic intervention in cancer and autoimmune disease. I am currently involved in the investigation of a series of secreted proteins over-expressed in tumors, with the aim to identify useful targets for the development of therapeutic antibodies for cancer treatment.

3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

4. Gene amplification is a process in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy, and is an important factor in the pathophysiology of cancer. Amplification of certain genes (e.g., Myc or Her2/Neu)

gives cancer cells a growth or survival advantage relative to normal cells, and might also provide a mechanism of tumor cell resistance to chemotherapy or radiotherapy.

5. If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan® PCR or the fluorescence *in situ* hybridization (FISH) assays -is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy. An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

6. I understand that according to the Patent Office, absent data demonstrating that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, gene amplification data are insufficient to provide substantial utility or well established utility for the gene product (the encoded polypeptide), or an antibody specifically binding the encoded polypeptide. However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that wiliful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: Avi Ashkenazi
Avi Ashkenazi, Ph.D.

Date: 9/15/03

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CURRICULUM VITAE

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July 2003

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Education:

1983:	B.S. in Biochemistry, with honors, Hebrew University, Israel
1986:	Ph.D. in Biochemistry, Hebrew University, Israel

Employment:

1983-1986:	Teaching assistant, undergraduate level course in Biochemistry
1985-1986:	Teaching assistant, graduate level course on Signal Transduction
1986 - 1988:	Postdoctoral fellow, Hormone Research Dept., UCSF, and Developmental Biology Dept., Genentech, Inc., with J. Ramachandran
1988 - 1989:	Postdoctoral fellow, Molecular Biology Dept., Genentech, Inc., with D. Capon
1989 - 1993:	Scientist, Molecular Biology Dept., Genentech, Inc.
1994 -1996:	Senior Scientist, Molecular Oncology Dept., Genentech, Inc.
1996-1997:	Senior Scientist and Interim director, Molecular Oncology Dept., Genentech, Inc.
1997-1990:	Senior Scientist and preclinical project team leader, Genentech, Inc.
1999 -2002:	Staff Scientist in Molecular Oncology, Genentech, Inc.
2002-present:	Staff Scientist and Director in Molecular Oncology, Genentech, Inc.

Awards:

1983:	First prize, The Boehringer Ingelheim Award

Editorial:

Editorial Board Member: Current Biology

Associate Editor, Clinical Cancer Research.

Associate Editor, Cancer Biology and Therapy.

Refereed papers:

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6. Protective efficiacy of TNF receptor immunoadhesin vs anti-TNF monoclonal antibody in a rat model for endotoxic shock. 5th International Congress on TNF. Asilomar, CA, May 1994.
7. Interferon-γ signals via a multisubunit receptor complex that contains two types of polypeptide chain. American Association of Immunologists Conference. San Franciso, CA, July 1995.
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16. Control of Apo2L signaling. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. Cold Spring Harbor, New York. September, 1997.
17. Chairman and speaker, Apoptosis Signaling session. IBC's 4th Annual Conference on Apoptosis. San Diego, CA., October 1997.
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51. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Kimmel Cancer Research Center, Johns Hopkins University, Baltimore MD. May 2002.
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53. Apoptosis signaling by Apo2L/TRAIL. (Session co-chair) TNF international conference. San Diego, CA. October 2002.
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Issued Patents:

1. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,329,028 (Jul 12, 1994).
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